The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000277.3(PAH):c.124_126del (p.Lys42del)

Version: 1.0

CA658821284

552279 (ClinVar)

Gene: PAH (HGNC:5053)
Condition: phenylketonuria (MONDO:0009861)
Inheritance Mode: Autosomal recessive inheritance
UUID: ed2c9ad7-42ed-4c37-92ee-bd4ee088e397
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HGVS expressions

NM_000277.3(PAH):c.124_126del (p.Lys42del)
NM_000277.3:c.124_126del
NC_000012.12:g.102912833_102912835del
CM000674.2:g.102912833_102912835del
NC_000012.11:g.103306611_103306613del
CM000674.1:g.103306611_103306613del
NC_000012.10:g.101830741_101830743del
NG_008690.1:g.9768_9770del
NG_008690.2:g.50576_50578del
ENST00000553106.6:c.124_126del
ENST00000307000.7:c.109_111del
ENST00000546844.1:c.124_126del
ENST00000548677.2:n.211_213del
ENST00000548928.1:n.46_48del
ENST00000549111.5:n.220_222del
ENST00000550978.6:c.108_110del
ENST00000551337.5:c.124_126del
ENST00000551988.5:n.213_215del
ENST00000553106.5:c.124_126del
ENST00000635500.1:n.92_94del
NM_000277.1:c.124_126del
NM_000277.2:c.124_126del
NM_001354304.1:c.124_126del
NM_001354304.2:c.124_126del

Likely Pathogenic

Met criteria codes 4

PM2 PM4 PP4 PM3_Strong

Evidence Links 2

Expert Panel

Phenylketonuria VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Phenylketonuria VCEP

The c.124_126del (p.Lys42del) PAH variant has been reported in 2 patients with PAH deficiency, detected with the pathogenic PAH variant p.Arg111Ter (PMID: 30050108) and the likely pathogenic PAH variant c.824C>T (PMID: 27243974). A defect in BH4 metabolism was not excluded. This variant is absent from population databases. The protein length changes as a result of an in-frame deletion in a non-repeat region. In summary, this variant meets criteria to be classified as likely pathogenic for PAH. PAH-specific ACMG/AMP criteria applied: PM2, PM3_strong, PM4, PP4.

Met criteria codes

PM2	✔	PM2_met: This variant is absent from population databases gnomAD and ExAC.
PM4	✔	PM4_met: Protein length changes as a result of an in-frame deletion in a non-repeat region.
PP4	✔	PP4_met: This variant was reported in 1 patient with PAH deficiency (PMID: 27243974) and 1 patient with classic phenylketonuria (PMID: 30050108) 27243974, Yubero - This variant was documented in 1 patient with PAH deficiency. To compare the diagnostic yield obtained after NGS, patients were classified into two groups depending on the level of evidence supporting the suspicion and independently of the NGS analysis results. Group 1 (n = 81) included patients who presented with consistent clinical and biochemical data supporting their having an IEM studied in the panel. This patient with this variant was a part of this group. Tetrahydrobiopterin (BH4) deficiency was not excluded through a BH4 loading test, urinary pterin analysis and DHPR activity assay. 30050108, Li - This variant was documented in 1 patient with classic phenylketonuria. Tetrahydrobipterin (BH4) deficiency was not excluded through a BH4 loading test, urinary pterin analysis and DHPR activity although that data was collected if available. PubMed:30050108 PubMed:27243974
PM3_Strong	✔	PM3_strong: This variant was detected in trans with a likely pathogenic variant in 1 patient with PAH deficiency (PMID:27243974) and with a pathogenic variant in 1 patient with classic phenylketonuria (PMID: 30050108) 27243974, Yubero - This variant was detected in trans with the likely pathogenic PAH variant c.824C>T (1 submission in ClinVar) in one patient with PAH deficiency. The inheritance of all of the patients with genetic findings was checked regarding their progenitors. 30050108, Li - This variant was detected in trans with the pathogenic PAH variant p.Arg111Ter (7 submissions in ClinVar including PAH EP) in 1 patient with classic PKU. Parental analysis was performed to confirm compound heterozygosity.

Curation History

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